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Luxturna and the new era of gene therapy in ophthalmology

Luxturna e a nova era da terapia gênica na oftalmologia

Fernanda Belga Ottoni Porto[1,2]

1. Doutorado em Oftalmologia pela Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil.
2. INRET Clínica e Centro de Pesquisa, Belo Horizonte, MG, Brazil.

On Thursday, August 6, 2020, a new era of profound changes for ophthalmology and medicine began in Brazil: the first gene therapy arrived in the country, with the approval of voretigene neparvovec (VN) (Luxturna™, Novartis) by the Brazilian Health Regulatory Agency (ANVISA).

VN is an associated adenovirus viral vector containing the human *RPE65* cDNA (AAV2-HRPE65v2), which is injected into the subretinal space after a pars plana vitrectomy in a hospital setting to treat inherited retinal disease (IRD) caused by variants in the two copies of the RPE65 gene. This gene encodes a protein that is essential to the visual cycle because it is responsible for converting all-trans-retinyl esters to 11-cis-retinol[1]. Deficiency of this protein results in the alteration of the visual cycle and consequent degeneration of photoreceptors, leading to progressive loss of vision. To date, 138 different variants in *RPE65* gene have been reported, of which 66% are associated with Leber congenital amaurosis (LCA) and 16% with retinitis pigmentosa (RP)[1], reflecting a phenotypic spectrum that ranges from profound congenital low vision of LCA and the milder symptoms of severe early childhood-onset retinal dystrophy to RP. Over time, patients with IRDs associated with untreated *RPE65* variants completely lose their ability to perceive light of any intensity[2]. The ability to walk independently becomes extremely limited, leading to the impossibility of performing daily-life activities that depend on vision[2].

The pivotal study that led to the approval of VN (Clinicaltrials.gov NCT00999609) included 31 patients with biallelic pathogenic *RPE65* variants. The patients were aged 3–44 years, and they were eligible for the clinical trial if they had visual acuity worse than 20/60 or a visual field of <20° from fixation. In the first year, patients were randomized 2:1 to receive bilateral treatment approximately every 18 days or to be followed for one year as a control group. At the end of the first year, patients in the control group would receive treatment if they continued to meet the inclusion criteria. The primary efficacy endpoint was the multi-luminance mobility test (MLMT), a type of test that evaluates the patient's ability to walk along a defined path with obstacles under varying degrees

Corresponding author: Fernanda B. O. Porto. E-mail: fernandabop@gmail.com
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of luminance. Performance improvement in MLMT was statistically significant in treated patients compared with that in the control group. Treated patients also had a mean improvement of 2 log in the full-field stimulus threshold test. Improvement was apparent 30 days after the procedure and remained stable for at least one year. Patients treated at Phase I of drug development suggest a sustained efficacy for up to 7 years[4] (Clinicaltrials.gov, NCT01208389). The adverse events related to the surgical procedure were: transient reversible elevation of intraocular pressure (20% of patients), cataracts (15% of patients), and retinal ruptures (10% of patients)[3].

The approval of VN has brought ophthalmologists and geneticists into a new era of precision therapeutic intervention and personalized medicine because it is now possible to modulate genetic diseases and modify their natural history. However, there are significant challenges that need to be addressed, such as the need for appropriate and accurate diagnosis and genetic counseling, preoperative management of expectations, and discussion of the risks and benefits associated with the treatment, especially with children. Not the least important concerns are cost and access to treatment as we enter the phase of non-investigative commercial treatment.

The use of Luxturna has accelerated several essential aspects of care of patients with hereditary retinal diseases as the molecular diagnosis determines the eligibility for the treatment with Luxturna or participation in clinical trials. The process of establishing a molecular diagnosis involves the characterization of the phenotype (the clinical picture resulting from the expression of the genotype) by a physician with expertise in hereditary retinal diseases. Currently, pathogenic changes in 25 genes have been identified as being able to cause LCA and in 90 genes as possible causes of RP (RETnet https://sph.uth.edu/retnet/). These genes account for 75% of LCA and RP cases. Current technology is still unable to detect changes in the remaining 25% of cases. When a causal gene is suspected, new variants identified must be thoroughly tested for confirmation of their pathogenicity, and segregation analyses need to be performed. Understanding whether a variant is inherited or *de novo* can affect the classification of the variant and the interpretation of the results; consequently, an incorrect understanding of the biological effect of the variant can lead to erroneous clinical interpretations and serious consequences. Drack et al.[5] presented several examples and a question: who should ideally request and explain the results of genetic tests? The consequences of an erroneous diagnosis go beyond offering an incorrect definition of the pathology or distorted information about the patient's health condition; they may result in providing ineffective treatment to some and failing to indicate treatment to others. Therefore, the rigorous multistep diagnostic process used in pivotal clinical trials should continue to be used for approved treatments.

The treatment of children requires additional considerations. Although they can benefit beyond visual gain, with the prospect of better social integration, they are still a vulnerable population. Children aged <5 years deserve special mention because postoperative examination for complications can be difficult and may require evaluation under narcosis to enable the identification and immediate treatment of potential complications. Secondary cataract formation can lead to amblyopia. In addition, the youngest child treated in the Phase III study was 3 years old, while the FDA has approved the treatment for children over 12 months of age. Therefore, the benefit of early intervention still needs to be investigated. Pretreatment parental guidance is essential to address any risk profile, with particular attention to the age at the time of treatment.

Cost and access to treatment remain to be the challenges in all countries where the drug has been approved. In Brazil, the medication has not yet been priced, but its cost in the United States is $425,000 per eye, with the second eye treatment within 6 days to minimize the risk of host immune response. Cost/benefit analysis using a modified social perspective considers the costs of medical care, education, loss of productivity, non-placement in the labor market, and related informal care. The single-dose treatment for each eye has aroused discussion about a new business model, even with uncertainty about the persistence of the treatment's effectiveness.

The clinical trials conducted in the development of Luxturna have brought several innovations. Because *RPE65*-related IRD primarily affects the rods, the measurement of visual acuity and optical coherence tomography (endpoints in studies of maculopathies such as age-related macular degeneration and macular edema), as well as autofluorescence (classic in studies on atrophic macular diseases) would not be applicable. New parameters have been developed for the evaluation of the disease process (endpoints),

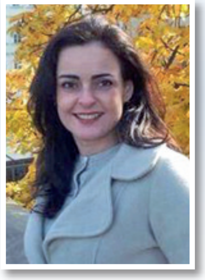
such as MLMT, which simultaneously assesses visual acuity, visual field, and retinal sensitivity to light, essential parameters for real-world navigation. It was necessary to define the stage of the course of the disease at which treatment with subretinal injections of VN should be indicated. To answer this, several issues needed to be addressed, including the treatment of pediatric patients in clinical trials, conducting parallel studies of natural history, determining the critical mass of photoreceptors, and establishing the severity of pathogenic variants and their effects on retinal trophism.

Even so, many questions will only be clarified after commercialization with the treatment of a larger number of patients followed longitudinally. What would be the response to treatment based on the subtype of mutation? What is the optimal age of intervention? What would be the long-term impact of treatment? Amid so many doubts, there is a certainty: ophthalmology and genetics in Brazil will never be the same after today.

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AUTHOR INFORMATION



» **Fernanda Belga Ottoni Porto**
https://orcid.org/0000-0002-4308-1766
http://lattes.cnpq.br/3705547122177092